WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 8, 271-284. Review Article ISSN 2277– 7105

AN OVERVIEW ON METFORMIN USE ANTICANCER DRUG THERAPHY

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Article Received on
04 May 2021,

Revised on 25 May 2021,
Accepted on 15 June 2021

DOI: 10.20959/wjpr20218-20739

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ABSTRACT

Metformin has been utilized for quite a while as an antidiabetic drug for type 2 diabetes. It is utilized either as a monotherapy or in mix with other antidiabetic meds. The medication became a force to be reckoned with in diabetes and different conditions with cardiovascular danger after the milestone investigation of 1995 by the United Kingdom Prospective Diabetes Study which accentuated its significance. Nonetheless, the medication has been utilized in trial preliminaries in different parts of medication and pharmacology, for example, in regenerative medication, malignant growth chemotherapy, metabolic sicknesses, and neurodegenerative illnesses. It has been being used in the treatment of polycystic ovarian sickness and weight and is being considered in type 1 diabetes. This investigation tries to assess the pertinence of metformin in malignant growth the board. Various systems have been proposed for its antitumor activity which includes the accompanying: (a) the initiation of adenosine monophosphate kinase, (b) regulation of adenosine A1 receptor (ADORA), (c) decrease in insulin/insulin development variables, and (d) the part of metformin in the restraint of endogenous receptive oxygen species (ROS); and its resultant harm to deoxyribonucleic corrosive (DNA) particle is another foremost antitumor component.

KEYWORDS: ADORA, ROS, DNA.

INTRODUCTION

Metformin is one of the broadly utilized oral antidiabetic medications. It has a place with the class called biguanides of which the different individuals have been removed due to related lactic acidosis. Metformin has been perceived as a first-line pharmacotherapy in type 2

diabetes the board in many guidelines, for example, American Diabetes Association.[1] The beginning of the medication isn't notable yet has been connected to a plant called Galega officinalis (goat's mourn), which is rich in guanidine.[2] The capacity of this home grown medication to decrease blood glucose was appeared in 1918. A portion of its derivatives aside from metformin were utilized to treat diabetes however were removed dependent on related poison levels.[3] Metformin came to spotlight in 1930 in the quest for antimalarial medications where it was found to have against flu and antidiabetic properties. Jean Sterne followed this revelation up, and in 1957, the utilization of metformin to treat diabetes was set up. In any case, the acknowledgment didn't proceed as metformin was less powerful than other biguanides (phenformin and buformin).[4] In reality, metformin was as it were authorized in the USA in 1994. Regardless of this, metformin was the most generally endorsed oral antidiabetic drug in the USA in 2012.[5] Metformin acts to bring down blood glucose basically by reducing hepatic gluconeogenesis, subsequently lessening glucose yield from the liver. It is a powerful glucose-bringing down specialist, lessening HbA1c by 10-15 mmol/mol (1.0-1.5%).[6] The milestone concentrate by the United Kingdom Prospective Diabetes Study (UKPDS) bunch in 1995 set up the long haul cardiovascular advantage of metformin, bringing about the resurgence in the pertinence of metformin in diabetes the board.[7]

Chemical Structure of Metformin

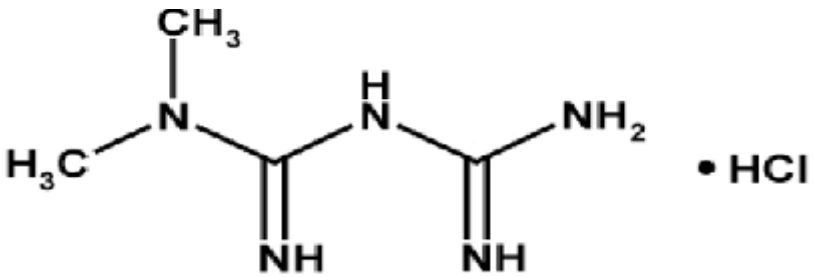

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Fig 1: Structure of metformin.

Metformin is an expert having a spot with the biguanide class of antidiabetics with antihyperglycemic activity. Metformin is connected with an especially low recurrence of lactic acidosis. This expert reduces LDL cholesterol and greasy substance levels, and isn't connected with weight procure, and thwarts the cardiovascular bothers of diabetes. Metformin isn't prepared and is released unaltered by the kidneys. Metformin is a first line specialist for the treatment of type 2 diabetes that can be utilized alone or in blend with sulfonylureas, thiazolidinediones, incretin-based medications, sodium glucose cotransporter-2

inhibitors, or other hypoglycemic specialists. Metformin has not been connected to serum protein heights during treatment and is a surpassing uncommon reason for eccentric clinically clear intense liver injury.[9]

Synthesis

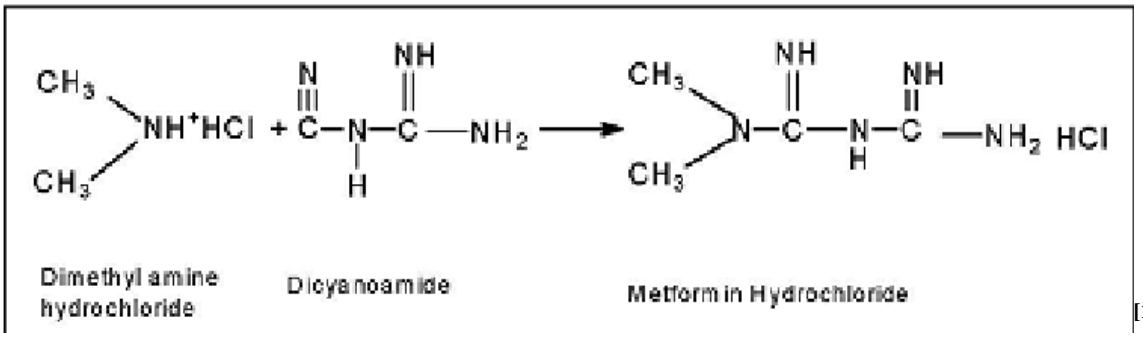

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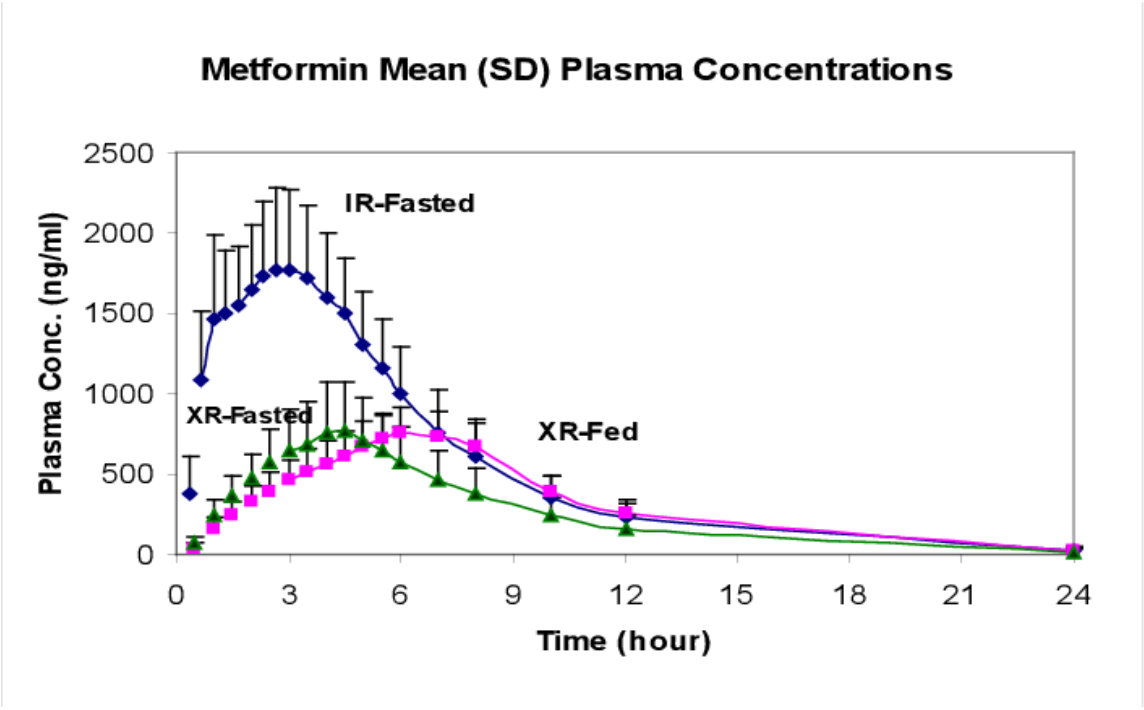
Fig 2: synthesis of metformin.

Pharmacokinetic Profile of Metformin

Metformin has an oral bioavailability of 50–60% under fasting conditions, and is retained slowly. [Peak plasma fixations (Cmax) are reached inside 1–3 hours of taking quick delivery metformin and 4–8 hours with broadened discharge formulations. The plasma protein restricting of metformin is unimportant, as reflected by its exceptionally high evident volume of dispersion (300–1000 l after a solitary portion). Consistent state is typically reached in 1–2 days. Metformin has corrosive separation steady qualities (pKa) of 2.8 and 11.5, so it exists generally as the hydrophilic cationic species at physiological pH esteems. The metformin pKa esteems make it a more grounded base than most other essential meds with under 0.01% nonionized in blood. Moreover, the lipid dissolvability of the nonionized species is slight as demonstrated by its low logP esteem (log[10] of the dissemination coefficient of the nonionized structure among octanol and water) of −1.43. These compound boundaries show low lipophilicity and, subsequently, fast uninvolved dispersion of metformin through cell layers is impossible. Because of its low lipid dissolvability it requires the carrier SLC22A1 with the goal for it to enter cells. The logP of metformin is not exactly that of phenformin (−0.84) in light of the fact that two methyl substituents on metformin bestow lesser lipophilicity than the bigger phenylethyl side chain in phenformin. More lipophilic subsidiaries of metformin are by and by being scrutinized fully intent on delivering prodrugs with predominant oral ingestion than metformin. Metformin isn't processed. It is cleared from the body by cylindrical discharge and discharged unaltered in the pee; it is imperceptible in blood plasma inside 24 hours of a solitary oral dose. The normal disposal half-life in plasma

is 6.2 hours.[90] Metformin is disseminated to (and seems to aggregate in) red platelets, with an any longer end half-life: 17.6 hours (detailed as going from 18.5 to 31.5 hours in a solitary portion investigation of nondiabetics). Some proof demonstrates that liver centralizations of metformin in people might be a few times higher than plasma fixations, because of entry vein assimilation and first-pass take-up by the liver in oral administration.[11]



[12]

Fig 2: Plasma drug profile metformin.

Mechanisms of Action of Metformin as an Anticancer Drug

Metformin and Mammalian Target of Rapamycin Complex 1.

Impediment of harm cell improvement by covering mammalian goal of rapamycin complex 1 (mTORC1). mTORC1 is a multiprotein complex which is made essentially of protein kinase mTOR and system protein raptor.[13] Adenosine monophosphate protein kinase (AMPK) can directly phosphorylate tuberous sclerosis complex (TSC2) on S1387, thusly propelling its restriction of mTORC1.[14] The stimulatory effect of protein combination by mTOR underlines its part in the processing and proliferation of compromising cells.[15,16]

Inception of Adenosine Monophosphate Protein Kinase

metformin shows its antineoplastic effect by incitation of adenosine monophosphate protein kinase (AMPK). This incorporates direct inhibition of mTORC1 through phosphorylation of S722 and S792 on the mTOR limiting raptor.[17] This resembles the arrangement of the

antidiabetic effect of metformin. The last incorporates liver kinase B1-(LKB1-) subordinate commencement of adenosine monophosphate-started protein kinase (AMPK).

Metformin and Inhibition of Generation of Reactive Oxygen Species (ROS)

The ROS hailing pathways are especially extended in various kinds of malignancies where they give climb to surprising increase and detachment. Responsive oxygen species consolidate peroxides, superoxides, hydroxyl radicals, singlet oxygen, and alpha oxygen.[18] The work of hydrogen peroxide, a normal delineation of ROS, is captured in reversible oxidation of tyrosine phosphatases, tyrosine kinases, and record factors.[19,20] The obstruction of ROS age is mediated by the movement of metformin on complex 1 of the respiratory chain which diminishes section of electron to the chain and over the long haul ROS creation.[21,22] The groupings of metformin expected to clearly control complex 1 molecule is high (20-100 mM) in isolated mitochondria in vitro . However, the in vivo restriction of complex 1 molecule can be achieved with micromolar centers.[23] The explanation relies upon the positive charge of metformin which grants moderate assortment inside the mitochondrial network.[28] The limitation of endogenous period of ROS is liberated from the AMPKα structure. One of the fundamental focal points of ROS-prompted cell hurt is the DNA with a resulting essential mutilation of its uprightness (change). Stream cytometry shows that cells pretreated with metformin can reduce ROS levels following paraquat transparency.[24]

Decrease of Serum Levels of Insulin, IGF-1, and IGF-2.

Metformin diminishes the degrees of upgrades that advance disease cell expansion.[25] Undeniable degrees of IGF-1 and IGF-2 are connected to the development of malignant growth or with disease repeat in malignant growth survivors.[26] The activities of IGF proteins are interceded by IGF-IR, a transmembrane tyrosine kinase which is basically identified with insulin receptor. The limiting of IGF-1 and IGF-2 on IGF-receptors in the end results in the initiation of mTOR which upgrades cell multiplication what's more, restraint of apoptosis.[27]

Restraint of Chronic Inflammation.

Metformin moreover hinders constant irritation, a cycle which is an important component in the inception and advancement of carcinogenesis.[28,29] Metformin restrains the underlying enactment of fiery reaction related with cell transformation and disease foundational microorganism development. This is identified with the inhibition of provocative record factor, NF-Kb.[30]

Tweak of Adenosine A1 Receptor (ADORA1)

Articulation portrayed another pathway included in the antineoplastic impact of metformin which includes the regulation of adenosine A1 receptor (ADORA1) articulation in human colorectal malignancy and bosom disease cells. ADORA1 receptors play fundamental in the stock of cell energy. Threatening cells are, hence, denied of energy in the course of downregulation of ADORA1 receptors. Metformin treatment apparently upregulates ADORA1 articulation in colorectal malignant growth cells.[31] The ADORA1-interceded development restraint and apoptosis instigated by metformin are AMPK-mTOR pathway subordinate in human colorectal malignancy cells.

Clinical Trials Using Metformin Hydrochloride in Cancer Therapy

Some clinical preliminaries with metformin are continuous to discover its impact in the treatment of various malignancies. Notwithstanding, a few preliminaries have been finished up. The preliminaries include metformin monotherapy or blend treatment with other chemotherapeutic specialist.

Table 1: clinical trials using metformin hydrochloride in cancer therapy.[32.33]

Cancer type	Phase	Primary outcome	Dosing regimen	Combination
Breast cancer	II	Effects of metformin on AMPK/m/TOR pathway	Metformin 1500 mg daily for 2 weeks before surgery	Metformin monotherapy
Breast, lung, liver, kidney	I	Effect of metformin+sirolimus on p70S6K	Sirolimus 3 mg daily for 1-7 days. Metformin 500 mg once daily for 8-21 days	Metformin, sirolimus
Colorectal	II	Disease control rate	FOLFOX+metformin/FOLFIRI+metformin	Metformin, FOLFOX6
Prostate	I	DLT assessed at 28days	Enzalutamide PO QD and metformin PO BID	Metformin, enzalutamide
Pancreas	II	PFS at 12 months	Everolimus+octreotide LAR+metformin	Metformin everolimus, octreotide LAR
Chronic lymphocytic leukemia	II	Time to treatment failure (assessed 3 months)	Metformin 500 mg PO QD, increased to 500 mg BID after 1week and to 1000 mg BID at week 3	Metformin monotherapy

SPECIFIC CANCERS

The positive effects of metformin have been shown in treatment and prevention of different specific cancers in various studies. The evidences of metformin effects in each cancer and the possible mechanisms are reviewed.

Colorectal Cancer

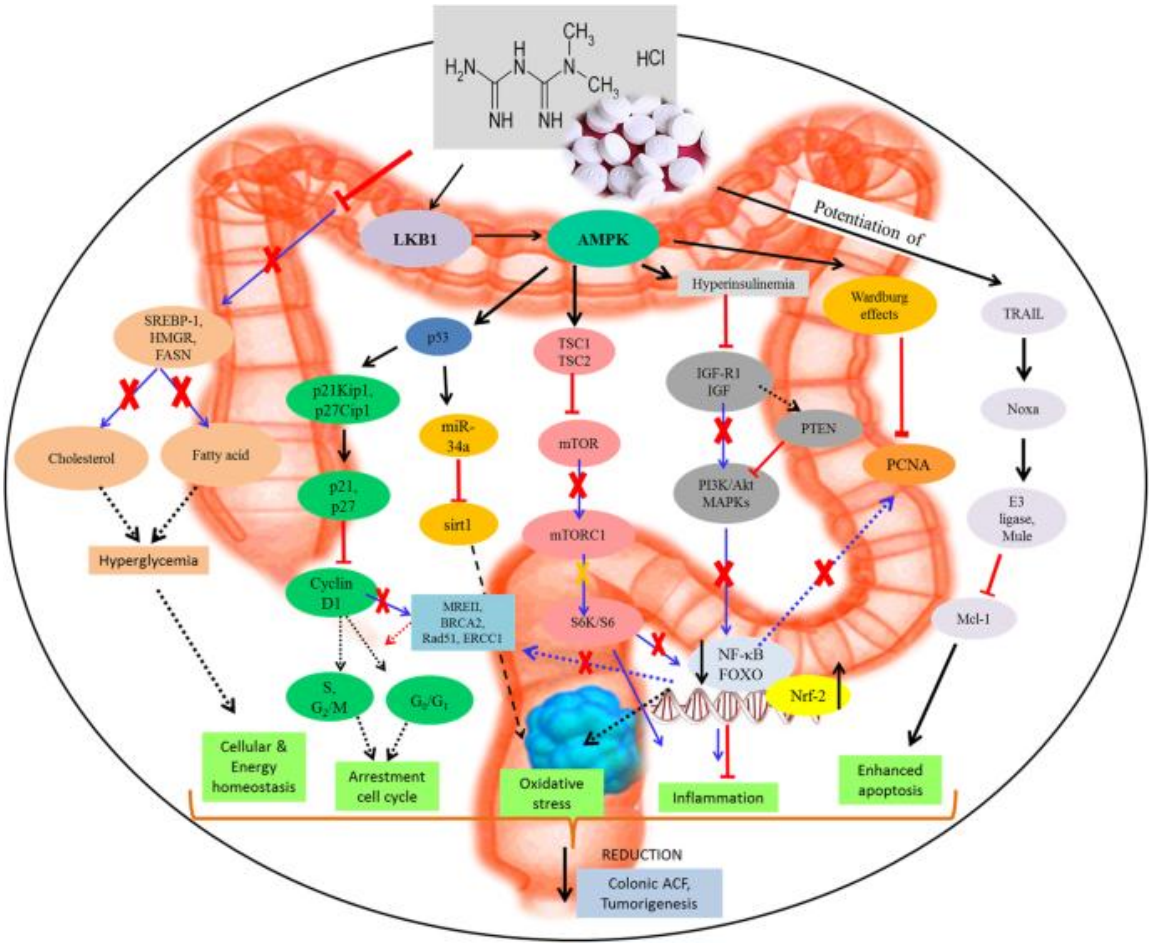


Fig 3: Metformin act colon cancer[36]

Advantages of metformin for anticipation and treatment of colorectal malignant growth have been appeared in a few examinations.[34] A new metainvestigation has shown that metformin improves generally endurance in diabetic patients with colorectal malignant growth. Hence, metformin is a great decision for the therapy of colorectal malignant growth in diabetic Patients.[35] Improved endurance of rectal malignancy has been seen in diabetic patients without metastasis who gone through remedial resection.

Pancreatic Cancer

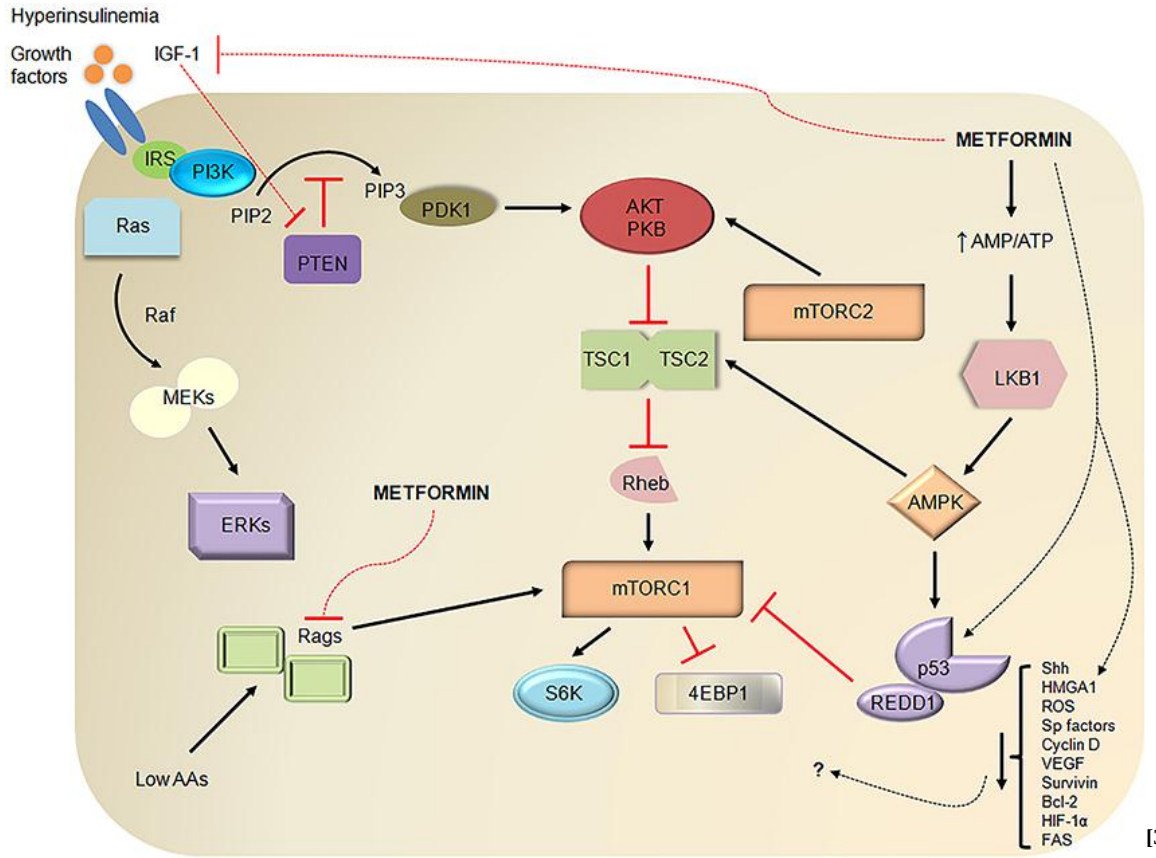


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Fig 4: Metformin act pancreatic cancer.

Metformin has been utilized for the therapy of pancreatic malignancy in a few examinations, yet the outcomes are conflicting.[36] In diabetic patients with pancreatic malignancy with confined resectable tu- mor, metformin diminishes the death rate. This advantage of metformin on pancreatic malignancy is portion subordinate Metformin restrains tumor development in pancreatic malignancy through diminishing desmoplastic response. It additionally improves the counter tumor impacts of pearlcitabine. These impacts are AMPK interceded. A few creators inferred that metformin has no impacts in Improving the endurance pace of patients with pancreatic malignancy.[38]

Brest Cancer

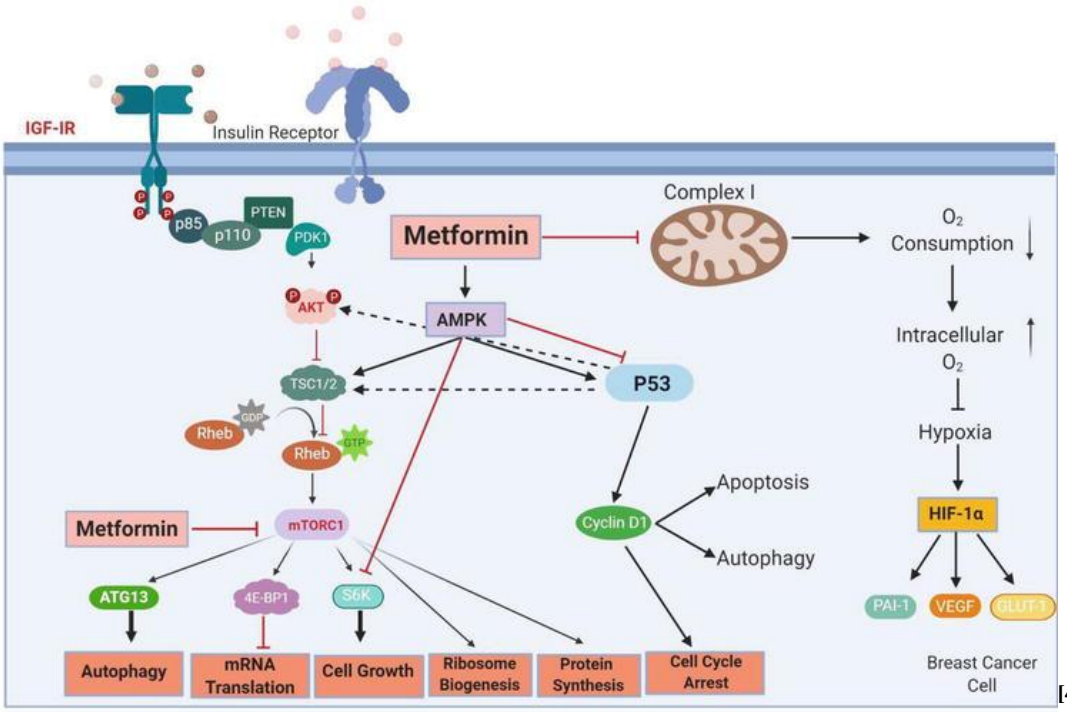

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Fig 5: Metformin act Brest cancer.

The job of metformin in the anticipation and treatment of bosom malignancy has been accounted for in a few investigations.[40] Nonetheless, the components are not completely perceived. Metformin was effectively utilized in blend with propranolol for control of triple negative bosom malignancy with no poisonousness. Likewise, the utilization of atenolol and ibuprofen was useful in bosom malignancy control. Treatment with metformin changed phospholipid digestion in patients with bosom malignancy.[41] Change in way of life and counteraction of weight acquire are significant factors in the avoidance of bosom malignancy. In diabetic patients, metformin utilization has been related with weight reduction. This may explain the motivation behind why metformin is gainful in the avoidance of bosom malignancy.[42]

Lung Cancer

Benefits of metformin on different types of lung cancer have been shown. Recent clinical trials have shown the beneficial effects of metformin on adenoma formation in lung cancer. The effect has been observed in both early and late stages of lung cancer. Adding pioglitazone to metformin had no additional benefits. Two recent meta-analysis studies have reported that using metformin improved the survival rate of lung cancer patients with diabetes mellitus.[44]

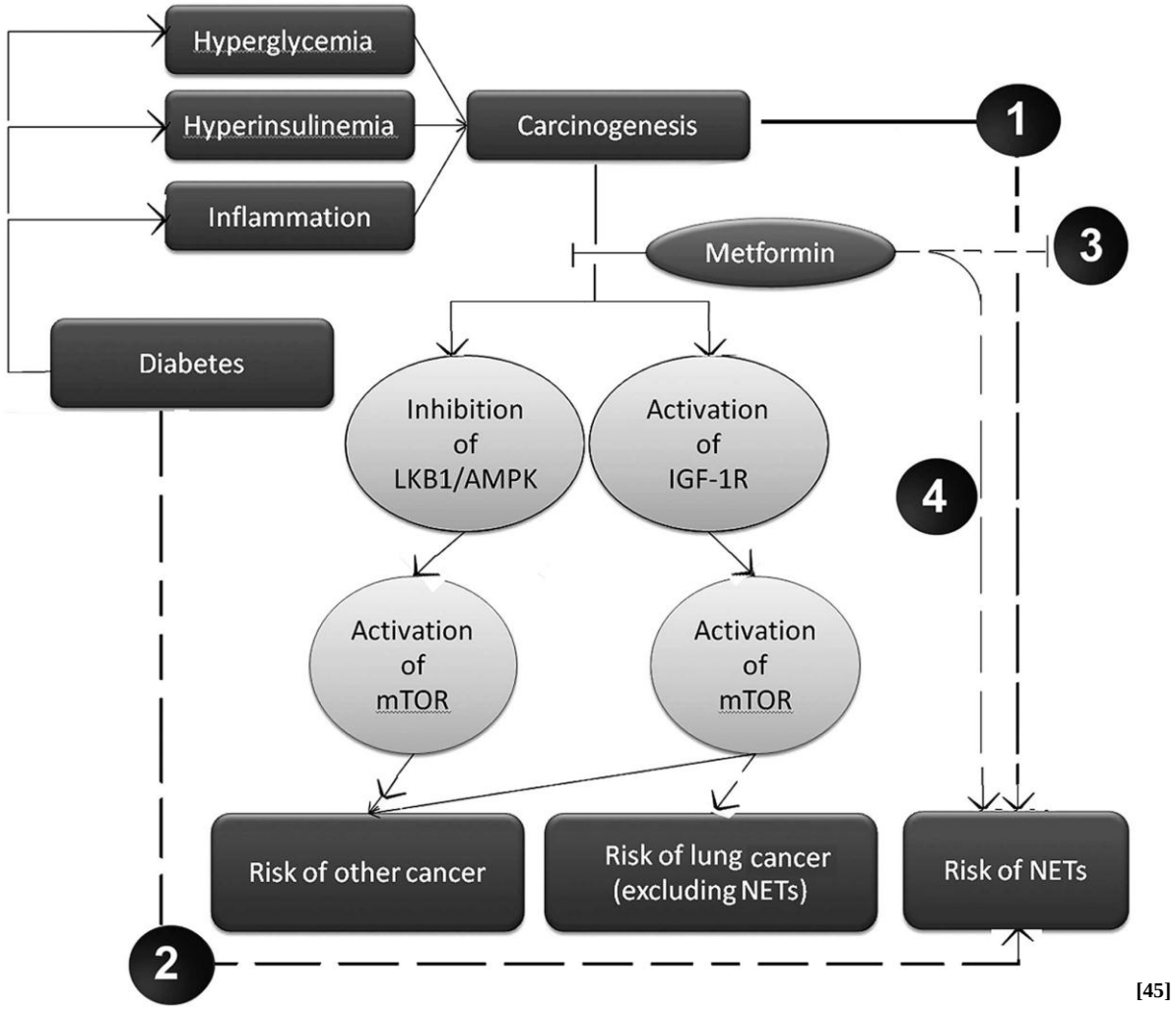

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Fig 4: Metformin act Lung cancer.

Gastric Cancer

In diabetic patients who were using metformin, a decreased risk for gastric cancer has been reported. The sonic hedgehog signaling pathway has an important role in gastric cancer pathogenesis. Metformin inhibits sonic hedgehog signaling pathway. This mechanism may explain the role of metformin in the prevention and treatment of gastric cancer.[46]

CONCLUSION

Metformin is notable for its utilization in the treatment of patients with diabetes mellitus. A few atomic properties like the hindrance of receptive oxygen species, mTORC1. ADORA and enactment of AMPK have recommended its utility as an antitumor specialist. A couple of clinical preliminaries have been conducted to research its utilization in certain tumors, yet results have not been empowering, however different preliminaries are as yet continuous. A few populace contemplates have recommended a defensive impact of metformin in the

disease of the bosom, colon, pancreas, prostate, and liver. Be that as it may, these have not obviously demonstrated a job for metformin as either a chemotherapeutic specialist or adjuvant treatment. As the aftereffects of continuous clinical preliminaries are anticipated, the creators recommend that further investigational exploration may zero in on approving these discoveries with the point of metformin use in disease chemotherapy even in nondiabetic patients too. Besides, connecting the metformin portion utilized in clinical medication with the fixation utilized in vitro may improve the clinical utility of metformin in neoplasms.

ACKNOWLEDGEMENTS

Author Offers A Sincere And Hearty Thanks, With A Deep Sense Of Gratitude To My Guide Mr.Ganesh Phadtare And, For Her Valuable Direction And Guidance To My work, Her Meticulous Attention Towards My Review Article Without taking Care Of Their Voluminous Work author Is Thankful To Our Principal Dr. Kishor Otari for His Encouragement Towards My Review Article. I Am Very Much Thankful to My Friend his Valuable Guidance, Keen Interest and encouragement At Various Stages of This Work. I Also Thank My Family For The Support Towards My Work.

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